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Award Number: W81XWH-08-2-0086

TITLE: The Separate and Cumulative Effects of TBI and PTSD on
Cognitive Function and Emotional Control

PRINCIPAL INVESTIGATOR: Diane Swick, Ph.D.

CONTRACTING ORGANIZATION:

Veterans Health Administration
Martinez, CA 94553-4668

REPORT DATE: April 2010

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

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REPORT DOCUMENTATION PAGE				Form Approved OMB No. 0704-0188	
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1. REPORT DATE (DD-MM-YYYY) 01/4/2010		2. REPORT TYPE Annual		3. DATES COVERED (From - To) 1 APR 2009-31 MAR 2010	
4. TITLE AND SUBTITLE The Separate and Cumulative Effects of TBI and PTSD on Cognitive Function and Emotional Control				5a. CONTRACT NUMBER W81XWH-08-2-0086	
				5b. GRANT NUMBER PT074597	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Diane Swick, Ph.D. Email: diane@ebire.org				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Veterans Health Administration 150 Muir Road Martinez, CA 94553-4668				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for public release; distribution unlimited.					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT In an emotional Stroop task, combat-related words were more distracting for Veterans with PTSD than for those without. We believe the test is a suitable measure of emotional reactivity and attentional bias that can be obtained before and after behavioral and pharmacological therapies. In addition, the patients showed a substantial deficit in motor response inhibition. Greater PTSD and depressive symptoms were both associated with worse performance on the motor task. The co-occurrence of mTBI and PTSD did not worsen the emotional and cognitive control difficulties associated with PTSD alone. Increased levels of impulsivity and a decreased ability to filter out distracting and emotionally intrusive information can negatively impact social and occupational functioning. In the future, computerized training interventions that target emotional and cognitive control skills may assist these OEF/OIF veterans in returning to their previous levels of productivity. The carefully-designed computerized tasks implemented in this project accurately assess the cognitive and affective sequelae of mTBI and PTSD.					
15. SUBJECT TERMS Cognitive Functioning, Traumatic Brain Injury, Post-Traumatic Stress Disorder					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT U	b. ABSTRACT U	c. THIS PAGE U			USAMRMC
			UU	13	19b. TELEPHONE NUMBER (include area code)

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INTRODUCTION: Combat veterans who have sustained a traumatic brain injury (TBI) can show impairments in behavioral and cognitive control and increases in impulsivity. In addition, many with mild TBI will also have post-traumatic stress disorder (PTSD). To improve diagnostic capabilities and better define treatment alternatives, it is important to determine the unique (and shared) contributions of each disorder to deficits in cognitive function and emotional control. Three specific control functions are being targeted: (1) **resolving conflict** between competing responses and competing aspects of a visual display; (2) **monitoring for errors** in performance and adjusting behavior accordingly; (3) **multi-tasking**, or the ability to maintain adequate performance in dual task situations. Converging evidence is obtained through the combined use of behavioral testing, electrophysiological recording (event-related potentials, ERPs), and structural imaging (diffusion tensor imaging, DTI). The project applies innovative methods by expanding the application of ERPs into the cognitive and behavioral domains most troublesome for patients with TBI and PTSD.

BODY: In the second year of the project, we enrolled 12 patients (total n=30) and 14 demographically-matched military control subjects (total n=18) and tested them on the first in a series of computer-based experiments that evaluate reaction time, cognitive processing, and emotional reactivity. In addition, we collected self-report information from 3 questionnaires. We have also tested 4 more civilian control participants (total n=12) to serve as another comparison group. We also collected data from 24 subjects in a second series of computerized experiments. Finally, we began recording EEG data in Exp. 2 and did preliminary work for Exp. 4. The research accomplishments associated with each task outlined in the approved Statement of Work are summarized below.

Project Timeline and Milestones		
	Year 1	Year 2
Patient Recruitment	ongoing	ongoing
Matched Controls	4	14
TBI only	1	1
PTSD only	6	2
TBI + PTSD	11	9
Pilot Studies	Exp. 1-2	Exp. 4
Behavioral Testing	Exp. 1	Exp. 1
ERPs		Exp. 2

Phase 1: Patient Recruitment: We enrolled 12 additional patients (all Veterans) into the study during the second year of the project (all male, mean age = 31 yrs). Of these, 10 had suffered one or more mild TBIs or probable TBIs (i.e., concussions) based on standard criteria from, e.g., the American Congress of Rehabilitative Medicine (ACRM, 1993) and WHO (Von Holst & Cassidy, 2004), as accepted by the VA and the DoD (see <http://www.pdhealth.mil/TBI.asp>). Eleven of the 12 Veterans enrolled in the project this year had received a PTSD diagnosis. Thus, of the three originally proposed patient groups, there are now a total of 20 in the TBI+PTSD group, 8 with PTSD only, and 2 with TBI only. Three additional participants who were recruited in Year 2 and enrolled in the study were excluded when it was learned they had experienced either childhood TBI or PTSD unrelated to military service.

We have been unsuccessful in recruiting a cohort of mTBI patients without PTSD. This is an issue that affects all investigators working with similar groups of OIF/OEF Veterans. The concern is whether an adequate sample of Veterans with mild TBI only, with no PTSD, can be found. In our experience thus far, most of the patients who meet the selection criteria for mild TBI (mTBI) also have a formal PTSD diagnosis. Our colleagues inform us that the same is true at the other major VANCHCS site in Sacramento. In addition, disagreement on the exact mTBI diagnostic criteria (both across and within sites) complicates the classification of enrolled patients. Furthermore, the definition of mTBI is under discussion at the moment (Hoge et al., 2009), and we are closely monitoring this debate. In addition to the patients, we have recruited 14 more demographically matched controls (Veterans, mean age = 34). We are continuing our concerted efforts to recruit a greater number of Veteran control subjects. Finally, participants completed 3 standardized questionnaires: the Barratt Impulsiveness Scale (BIS), the PTSD Checklist – Military (PCL-M), and the Beck Depression Inventory (BDI).

One ultimate goal of the current project is to combine MRI and EEG brain imaging methods with carefully designed behavioral tasks to improve patient diagnosis. To this end, our collaborator, Dr. And Turken, has obtained DTI data from 11 patients and 15 Veteran controls as part of his VA Career Development Award project. Data collection and data analysis in his project are ongoing.

Phase 2: Pilot Studies: An EEG experiment to be conducted in Year 3 is designed to look at the effects of multitasking on attention and performance monitoring (Exp. 4). Additional analyses of previously collected data examined the effects of dual task performance (working memory load of 4 or 7 letters) on brain activity related to attention in control subjects (Pratt et al., 2010). This study looked at brain waves (event-related potentials, or ERPs) during a flanker interference task under 3 conditions: single-task, load 4, and load 7. It was especially interesting that dual task performance at either load resulted in a decrement of early visual attention: the P1 component recorded at occipital lobe electrodes was diminished (Fig 1).

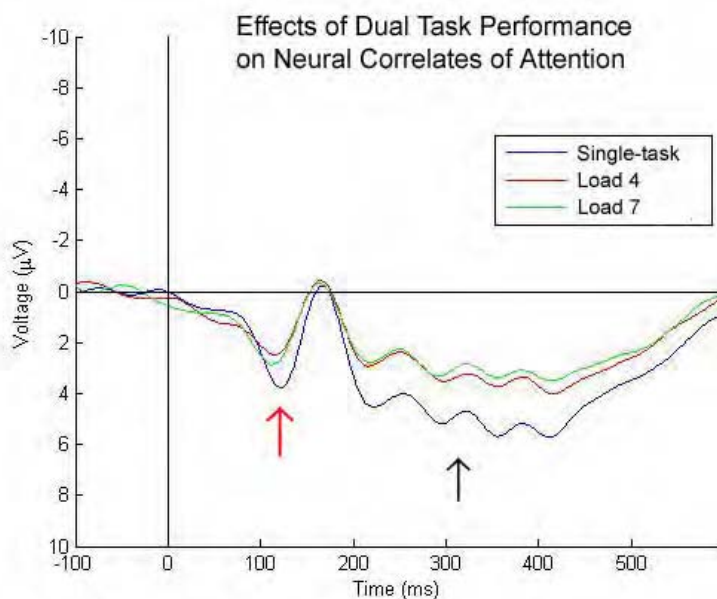


Fig. 1 – ERPs recorded at the left occipital electrode (O1) during performance of a flanker interference task under conditions of no distraction (Single-task), a working memory load of 4 letters (Load 4), and a working memory load of 7 letters (Load 7). The early visual P1 component at 120 msec (red arrow) and the extended P2-P3 complex (black arrow) were both sensitive to diversion of attentional resources.

This finding suggests that the prefrontal cortex typically provides a top-down signal to boost sensory processing in visual cortical regions. Under distracting dual-task conditions, frontal lobe attention and working memory processes were diverted from the primary task to perform the secondary task. In addition, the Load 4 and Load 7 conditions did not differ from each other, indicating that the secondary task of keeping 4 items in working memory was sufficient to disrupt both early and late attention. We are in the process of adjusting the working memory parameters to Load 1 and Load 4 for the current population of PTSD/TBI patients and testing this in several control subjects. The question for this project is whether Veterans with mild TBI and PTSD will show reductions in visual attention ERPs in the single-task condition that are comparable to those seen in control subjects in the dual-task conditions.

Phase 3: Behavioral Testing: Testing and data analysis in the emotional Stroop task (Exp. 1) are ongoing and will be completed during the first half of Year 3. The Go/NoGo task is another executive control task that provides a measure of response inhibition, and a paper describing those findings will soon be submitted for publication. Results from these studies are summarized below.

Experiment 1 – Emotional Stroop task with Combat-Related Words:

This experiment was designed to be an objective behavioral measure that may be able to distinguish between combat veterans with a PTSD diagnosis and those without. It is a variant of the color word Stroop task, in which participants name the font color of words presented on the screen while ignoring the words themselves. In our current paradigm, the words are presented in blocks of negative emotional words, positive emotional words, combat-related words, and appropriately matched neutral words. The metrics of interest are reaction times (RTs) for naming the color of combat words relative to neutral words, as the former are thought to divert attention away from the primary task in Veterans with PTSD. The patients were compared to a group of 16 demographically matched military control participants.

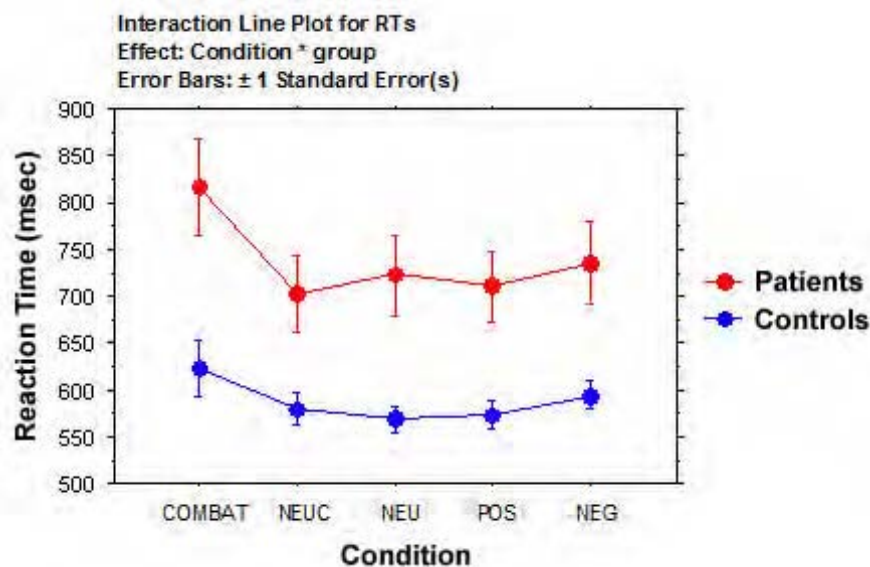


Fig. 2 – Color naming reaction time for the five different stimulus conditions: COMBAT = combat-related words; NEUC= neutral words matched to combat; NEU = neutral words matched to negative words; POS = positive emotional words; NEG = negative emotional words.

The patients were significantly slower overall (Fig. 2) at color naming relative to controls

[$F(1,40)=7.44$, $p<.01$]. This was due to a clear emotional Stroop effect (slowing of RTs) for combat-related words in the PTSD patient group [main effect of condition: $F(4,100)=12.01$, $p<.0001$] that was larger than in the controls [$F(4,60)=3.13$, $p<.05$]. Pairwise comparisons of combat-related words vs. neutral words revealed a highly significant effect for the PTSD patients ($p<.0001$), but only a trend in control subjects ($p=.07$). Conversely, comparing the RTs for non-combat negative words (e.g., TORNADO, POISON, CONTEMPT) vs. neutral words (RETIRED, PENCIL, CABBAGE) did not yield a significant emotional Stroop effect in the patients ($p=.43$) but did reveal a trend in controls ($p=.06$). Some prior studies have observed such an effect in non-clinical populations (e.g., Ashley & Swick, 2009), but many have not (reviewed in Phaf & Kan, 2007; Williams et al., 1996).

The most important finding is the combat-specific emotional Stroop effect in the OEF/OIF Veterans with PTSD. Previous studies have demonstrated the emotional Stroop effect in clinical populations, in which words related to an area of concern for an individual (i.e., snakes or spiders for phobics) elicit slower response times than neutral or even other emotional words (Williams et al., 1996). In comparison to previous studies on PTSD, the mean size of the interference effect that we observed (114 msec) is large (Shin et al., 2001; Wingenfeld et al., 2009) and comparable to the combat Stroop study of Constans et al. (2004). The difference in RT between combat and neutral words was calculated to provide a direct comparison between the size of the combat Stroop effects in the PTSD and control groups (Fig. 3).

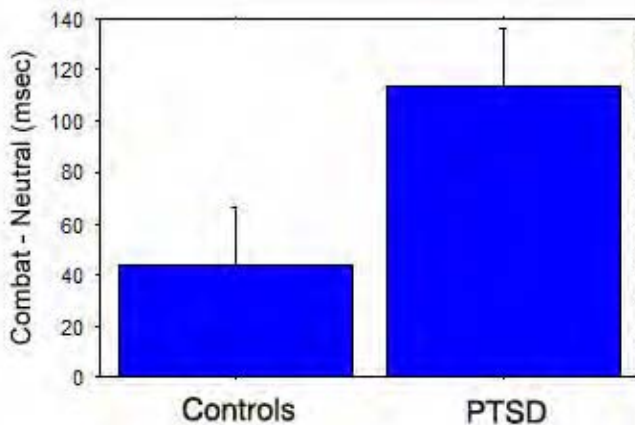


Fig. 3 – Size of the emotional Stroop effect for combat-related words, calculated as the differences in response times for naming the color of combat words minus neutral words (in msec).

The difference between controls and PTSD patients was significant ($p<.05$). Importantly, Veterans with TBI+PTSD did not differ from Veterans with PTSD only, suggesting that additional mTBI did not compound the attentional bias effect associated with PTSD. In addition, there were no significant correlations between the size of the combat Stroop effect and scores on the PCL-M ($p=.08$) or the BDI ($p=.17$). However, of the three PTSD symptom clusters (re-experiencing, avoidance/numbing, hyperarousal), there was a modest correlation with the re-experiencing subscale ($p=.02$). Although preliminary, the emotional Stroop task shows promise as an objective measure of PTSD symptomology.

Go/NoGo Task – Motor Response Inhibition:

This task measures a person's ability to inhibit an inappropriate response, a key function attributed to the frontal lobes and a major component of executive control (Miyake et al., 2000).

Single letters were rapidly presented on a computer screen, and subjects were instructed to respond as quickly as possible to any letter except “X,” the NoGo stimulus. The difficulty of the task was manipulated by altering the probability of “Go” trials relative to “NoGo” trials, i.e., 50% Go trials vs. 90% Go trials (with 50% NoGo vs. 10% NoGo, respectively). Performance measures (error rates and reaction times) from the patient group (n=30) were compared to those from an age-matched Veteran control group (n=18). All participants made more errors on the difficult condition [$F(1,46)=106.21$, $p<.0001$], when the need to inhibit responses was rare (Fig. 4). The patients were significantly impaired on this task overall, committing more errors in both conditions [$F(1,46)=11.76$, $p<.002$]. Furthermore, “Go” probability interacted with group [$F(1,24)=4.74$, $p<.05$]. RTs did not differ between the groups (p 's>.3), suggesting that a speed-accuracy trade-off in the patients cannot account for their deficit.

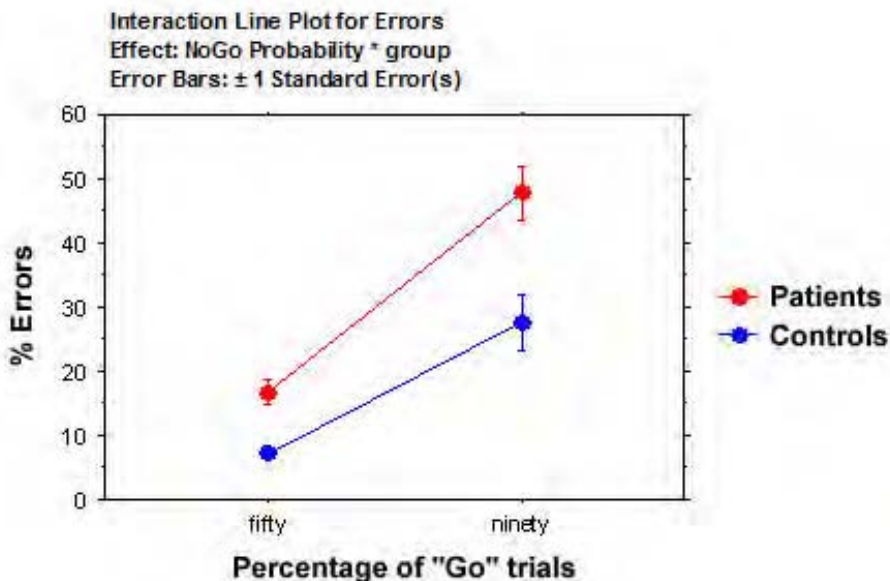


Fig. 4 – Percentage of errors on the GoNoGo task for both conditions (which were presented in separate blocks). The “fifty” condition means that “Go” trials requiring a button press response occurred on 50% of the trials, and the “ninety” condition means that “Go” trials occurred on 90% of the trials.

Veterans with TBI+PTSD did not make more mistakes on this task than Veterans with PTSD only, suggesting that additional mTBI did not compound the response inhibition deficit associated with PTSD. There were only two patients with mild TBI without PTSD in our patient pool. However, Nelson and colleagues (2009) found that OEF/OIF Veterans with mTBI+PTSD performed worse than those with mTBI without PTSD on speed of processing and executive function tasks.

Furthermore, self-rated impulsivity on the Barratt Impulsiveness Scale (BIS) did not correlate with performance in the 50% Go condition ($p=.12$) or in the 90% Go condition when responses were harder to inhibit ($p=.25$), which was surprising. Nor was there any correlation with the motor subscale of the BIS, which was expected to be most relevant for the Go/NoGo task. Although this questionnaire is one of the most commonly used measures of impulsivity (Spinella, 2007), it has not yet been validated in participants with mild TBI and PTSD. In addition, a recent study suggests that neurocognitive measures may not correlate with the BIS (Wu et al., 2009). Instead, scores on the BDI and PCL-M showed a much better correlation with performance: more severe levels of depression (Spearman’s $\rho=.43$, $p=.003$) and PTSD

symptoms ($\rho=.42$, $p=.004$) were both associated with higher error rates in the 90% Go condition. Finally, the striking correlation between PCL-M and BDI scores was notable ($\rho=.85$, $p<.0001$), indicating that PTSD and depression showed a high level of co-morbidity in these OEF/OIF Veterans.

Interestingly, previous GoNoGo results in TBI patients have been mixed. Some papers have reported deficits (Robertson et al., 1997), while others have not (Whyte et al., 2006). We recently reported that a group of moderate to severe TBI patients with lesions to orbitofrontal cortex were not impaired in this task (Swick et al., 2008). On the other hand, civilians with PTSD (and no TBI) showed an increased error rate and reduced recruitment of frontal cortical regions in a neuroimaging study of response inhibition (Falconer et al., 2008). Taken together, these results suggest that PTSD symptoms interfere with effective response inhibition. Our prior work demonstrated that stroke patients with focal lesions in the left inferior frontal gyrus showed a pattern of impairment similar to that reported here (Swick et al., 2008). However, the present group of OIF/OEF Veterans had an even greater deficit in motor response inhibition, which can have important implications for daily life. Thus, the Go/NoGo task provides a measure of inhibitory control that is more objective than self-reported evaluations of behavioral tendencies.

Phase 4: ERP Studies:

EEG data collection in Experiment 2 is ongoing (Fig. 5). The plot below shows the averaged event-related potentials (ERPs) from 10 control participants in the flanker interference task, which is related to Stroop-type interference tasks and response inhibition tasks such as the Go/NoGo (Swick et al., 2008).

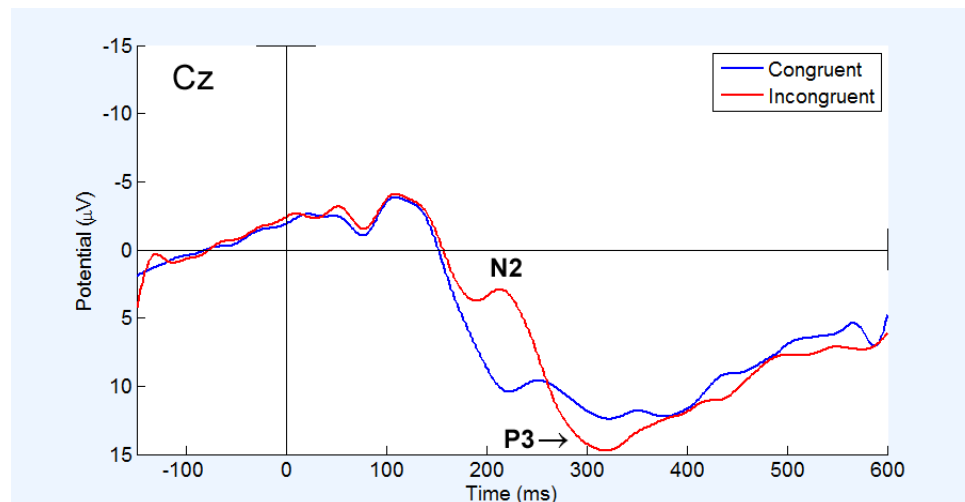


Fig. 5 – The N2 and P3 components recorded from 10 controls in the flanker interference task. These ERPs (from the central midline electrode Cz) were time-locked to stimulus onset (congruent trials in blue, incongruent trials in red). Negative is plotted upwards.

The N2 component was generated when the visual display indicated conflicting response options, as when the central target arrow and flanking distractor arrows pointed in opposite directions:

→ → ← → →

The conflict-related N2 component was followed by a larger P3 component, indicative of greater attention allocation. Also of interest are the electrophysiological responses on error trials. The

error-related negativity (ERN) and error positivity (Pe) components are associated with the commission of errors in choice reaction time tasks. We previously demonstrated that patients with moderate to severe TBI showed significant reductions in the amplitude of the ERN and in error correction performance (Turken & Swick, 2008). In Year 3, we will examine whether mild TBI and PTSD alter the integrity and timing of attentional control processes in the brain using these ERP measures.

KEY RESEARCH ACCOMPLISHMENTS:

- Enrolled 12 OEF/OIF Veterans with PTSD and/or mTBI and 14 Veteran control participants into the study.
- Began recording ERPs for Exp. 2 and began collecting ERP pilot data for Exp. 4.
- Demonstrated that the emotional Stroop task with combat-related words is a robust and sensitive measure of attentional bias to trauma-relevant material in OEF/OIF Veterans with PTSD. The addition of mTBI(s) did not compound this attentional bias effect.
- Found that OEF/OIF Veterans with PTSD exhibited an impulsive response style in a Go/NoGo task that measures the ability to inhibit inappropriate responses. The co-occurrence of mTBI and PTSD did not worsen the response inhibition deficit associated with PTSD alone. The severity of self-rated PTSD and depressive symptoms correlated with the degree of behavioral impairment on the task.
- Presented an earlier version of these behavioral findings as poster and slide presentations at the Military Health Research Forum.
- Submitted for publication a paper comparing the neural correlates of two different response inhibition tasks, based on a meta-analysis of the neuroimaging literature. Clarifying the brain regions that implement performance of the Go/NoGo task will help identify the neural networks compromised in those with PTSD.
- Prepared one publication on the response inhibition deficit associated with PTSD/mTBI, and another paper on how multitasking affects behavioral and neural measures of visual attention in control participants.

REPORTABLE OUTCOMES:

Abstract

Pratt N, Willoughby A, Swick D. When the going gets tough, attention starts going. Abstract submitted in Nov. 2009. Poster presented at the Cognitive Neuroscience Society meeting, April 17-20, 2010. http://www.cnsmeeting.org/index.php?Page=poster_detail.php&ID=304

Presentations

September 3, 2009: Attentional Bias and Response Inhibition in Veterans with Post-Traumatic Stress Disorder and Traumatic Brain Injury. Military Health Research Forum, Kansas City.

August 18, 2009: Neurobehavioral Brown Bag Lunch (NBBL) at VANCHCS in Martinez.

December 17, 2009: Neurology Grand Rounds at the University of California, Davis Medical Center in Sacramento.

Publications

Swick D, Ashley V, Turken AU. (submitted). Are the neural correlates of stopping and not going identical? Quantitative meta-analysis of two response inhibition tasks.

Swick D, Pratt N, Larsen J, Ashley V. (in preparation). Impaired response inhibition and cognitive control in veterans with post-traumatic stress disorder and mild traumatic brain injury.

Related Publication - This work was funded by the PI's VA Merit grant and is directly relevant to the present DoD project:

Pratt N, Willoughby A, Swick D. (in preparation). Top-down attentional control over early visual processing is diminished by increasing demands in working memory.

CONCLUSIONS: Trauma-relevant words captured attention to a greater extent in Veterans with PTSD than in those without. Thus, the emotional Stroop test shows promise as an objective behavioral measure that may be able to distinguish between OEF/OIF combat Veterans with a PTSD diagnosis and those without. We believe it is a suitable test of emotional reactivity and attentional bias that can be obtained before and after behavioral and pharmacological therapies. In addition, the present group of patients showed a substantial deficit in motor response inhibition, which can have implications for daily life. Greater PTSD and depressive symptoms were both associated with worse performance on the task. The co-occurrence of mTBI and PTSD did not worsen the emotional and cognitive control difficulties associated with PTSD alone. Increased levels of impulsivity and a decreased ability to filter out distracting and emotionally intrusive information can negatively impact social and occupational functioning. In the future, computerized training interventions that target emotional and cognitive control skills may assist these OEF/OIF veterans in returning to their previous levels of productivity. The carefully-designed computerized tasks implemented in this project accurately assess the cognitive and affective sequelae of mTBI and PTSD.

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